SEARCH REQUEST FORM

Examiner # (Mandatory): 72399 Requester's Full Name: 10 Stock 18 Art Unit 1020 Location (Bldg/Room#): REM 5AM Phone (circle 305 306 308) Serial Number: 10 784 917 Results Format Preferred (circle) PAPER DISK E-MAIL Title of Invention SEE ATTACHED BYS
Inventors (please provide full names): SEE ATTACHED BIB
Earliest Priority Date: SEE ATTRCHED BIB Keywords (include any known synonyms registry numbers, explanation of initialisms):
Search Topic: Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).
Claims attached - claims Itad Bonly elected species (see attached) Core:
Searcher:



STIC Search Report Biotech-Chem Library

STIC Database Tracking Number 1995

TO: Laura Stockton

Location: REM/5A01/5C18

Art Unit: 1626

Friday, August 19, 2005

Case Serial Number: 10/784917

From: Mary Hale

Location: Biotech/Chem Library

Rem 1D86 Phone: 2-2507

Mary.Hale@uspto.gov

Search Notes

Feel free to contact me if you have any questions.

Note -- results are printed on both sides of printout



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Page 1
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      (FILE 'HOME' ENTERED AT 14:56:18 ON 19 AUG 2005)
      FILE 'REGISTRY' ENTERED AT 14:58:18 ON 19 AUG 2005
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 L2
               0 S L1
 L3
               1 S L1 FUL
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 L11
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             522 FILE CAPLUS
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 L17
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 L19
         1419137 FILE EMBASE
 L20
         3099346 FILE CAPLUS
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 L21
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L22
L23
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             157 FILE CAPLUS
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L35
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L42
            1354 FILE MEDLINE
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L53
L54
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L55
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L57
L58
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L60
              3 FILE CAPLUS
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L62
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L67
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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STRUCTURE FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6 DICTIONARY FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at: http://www.cas.org/ONLINE/DBSS/registryss.html

L1 STR

X 18

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15 C 8 0 17 14

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16 C 4 N 9

5

NODE ATTRIBUTES: DEFAULT MLEVEL IS ATOM DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES: RING(S) ARE ISOLATED OR EMBEDDED NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L3 1 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 5 ITERATIONS SEARCH TIME: 00.00.02

YOU HAVE REQUESTED DATA FROM FILE 'BIOSIS, CAPLUS' - CONTINUE? (Y) /N:n

1 ANSWERS

=> fil medl, biosis, embase, caplus; d 18 ibib abs hitstr

COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION FULL ESTIMATED COST 0.43 745.85 DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL ENTRY SESSION CA SUBSCRIBER PRICE 0.00--5.11

FILE 'MEDLINE' ENTERED AT 15:10:27 ON 19 AUG 2005

FILE 'BIOSIS' ENTERED AT 15:10:27 ON 19 AUG 2005 Copyright (c) 2005 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 15:10:27 ON 19 AUG 2005

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ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN L.S

ACCESSION NUMBER:

1998:147306 CAPLUS

DOCUMENT NUMBER:

128:204803

TITLE:

Indolinone combinatorial libraries and related products and methods for the treatment of disease

INVENTOR(S):

Tang, Peng Cho; Sun, Li; McMahon, Gerald; Hirth, Klaus

Peter; Shawver, Laura Kay; et al.

PATENT ASSIGNEE(S):

Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon,

Gerald

SOURCE:

PCT Int. Appl., 293 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

12

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	TENT	NO.											DATE				
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		PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,	UA,	ŪĠ,	US,
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				US	1997-45714P	P	19970505
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				ΕP	1997-939480	A3	19970820
				WO	1997-US14736	W	19970820

OTHER SOURCE(S):

MARPAT 128:204803

Ι

AΒ The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. The compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepared by combinatorial condensation of certain (un) substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro. IT 204004-29-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and testing of indolinone combinatorial library as protein kinase inhibitors)

RN 204004-29-5 CAPLUS

CN

2H-Indol-2-one, 5-amino-3-[(3,4-dibromo-5-methyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} H & O & H \\ \hline M & CH & N \\ \hline \\ Br & Br \\ \end{array}$$

REFERENCE COUNT:

15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
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FULL ESTIMATED COST	7.94	753.79
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CA SUBSCRIBER PRICE	-0.73	-5.84

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STRUCTURE FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6 DICTIONARY FILE UPDATES: 18 AUG 2005 HIGHEST RN 860995-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at: http://www.cas.org/ONLINE/DBSS/registryss.html

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Page 7
L9
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NODE ATTRIBUTES:
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DEFAULT ECLEVEL IS LIMITED
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NUMBER OF NODES IS 12
STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01
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           5788 S L9 FUL
     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG 2005
L12
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L13
            337 FILE BIOSIS
L14
            964 FILE EMBASE
L15
            522 FILE CAPLUS
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L16
           1859 S L11
L17
        2428283 FILE MEDLINE
L18
        3250801 FILE BIOSIS
L19
        1419137 FILE EMBASE
        3099346 FILE CAPLUS
L20
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       10197567 S (PHARMAC? OR COMBINATOR? LIBRAR? OR COMPOS?)
L22
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L26
           1225 S L16 AND L21
L27
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L28
         365178 FILE BIOSIS
L29
         145295 FILE EMBASE
L30
        147528 FILE CAPLUS
     TOTAL FOR ALL FILES
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1 FILE MEDLINE

844702 S (TREAT? OR PREVENT? OR THERAP?) (5A) DISEASE?

L31

L32

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Page 8
L33
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L34
             85 FILE EMBASE
L35
             43 FILE CAPLUS
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L37
            447 FILE MEDLINE
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            943 FILE CAPLUS
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L42
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L43
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L44
           1108 FILE EMBASE
L45
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L72
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     FILE 'REGISTRY' ENTERED AT 15:09:50 ON 19 AUG 2005
     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:10:27 ON 19 AUG 2005
     FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005
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ibib abs
COST IN U.S. DOLLARS
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FULL ESTIMATED COST 1.29 755.08

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL ENTRY SESSION CA SUBSCRIBER PRICE 0.00 -5.84

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L62 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:168826 BIOSIS DOCUMENT NUMBER: PREV200400170685

TITLE: 3-(piperazinylbenzylidenyl)-2-indolinone compounds and

derivatives as protein tyrosine kinase inhibitors.

AUTHOR (S): Tang, Peng Cho [Inventor, Reprint Author];

Sun, Li [Inventor]; McMahon, Gerald

[Inventor]; Shawver, Laura Kay [Inventor]; Hirth,

Klaus Peter [Inventor] CORPORATE SOURCE: Forest City, CA, USA ASSIGNEE: Sugen, Inc.

PATENT INFORMATION: US 6696448 20040224

SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (Feb 24 2004) Vol. 1279, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).

DOCUMENT TYPE: Patent

LANGUAGE: English

ENTRY DATE: Entered STN: 24 Mar 2004

Last Updated on STN: 24 Mar 2004

The present invention relates to novel 3-(piperazinyl-benylidenyl)-2indolinone compounds and derivatives and physiologically acceptable salts thereof which are expected to modulate the activity of protein tyrosine kinases and therefore to be useful in the prevention and treatment of protein tyrosine kinase related cellular disorders such as cancer.

L62 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:262328 BIOSIS PREV200100262328 DOCUMENT NUMBER:

TITLE: Indolinone combinatorial libraries and related products and

methods for the treatment of disease.

AUTHOR (S): Tang, Peng Cho [Inventor]; Sun, Li

[Inventor]; McMahon, Gerald [Inventor]; Hirth, Klaus Peter [Inventor]; Shawver, Laura Kay

[Inventor, Reprint author]

CORPORATE SOURCE: San Francisco, CA, USA

ASSIGNEE: Sugen, Inc.

PATENT INFORMATION: US 6147106 20001114

SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (Nov. 14, 2000) Vol. 1240, No. 2. e-file.

CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent LANGUAGE: English

LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2001

Last Updated on STN: 19 Feb 2002

The present invention relates to organic molecules capable of modulating, regulating and/or inhibiting protein kinase signal transduction. Such compounds are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis and restenosis and metabolic diseases such as diabetes. The present invention features indolinone compounds that potently inhibit protein kinases and related products and methods. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3-yl)methylene]-2indolinone, in particular at the 1' position of the indole ring. Indolinone compounds that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano-b-pyrrol moiety. Indolinone compounds that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosoluble indolinone compounds that are tyrosine kinase inhibitors and related products and methods.

L62 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999

1999:626172 CAPLUS

DOCUMENT NUMBER:

131:257441

TITLE:

Heterocyclic families of compounds [tricyclic-based

indolinones and pyrazolecarboxylic acid amides] for

the modulation of tyrosine protein kinase

INVENTOR (S):

Fong, Annie; Hannah, Alison; Harris, David G.; Hirth, Peter; Hubbard, Steven R.; Langecker, Peter; Liang,

Congxin; McMahon, Gerald; Mohammadi, Moosa;

Schlessinger, Joseph; Shawver, Laura K.; Sun, Li; Tang, Peng C.; Ullrich,

Axel

PATENT ASSIGNÉE(S):

Sugen, Inc., USA; New York University; Max-Planck

Institut fur Biochemie PCT Int. Appl., 269 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

SOURCE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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    US 2003203901
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                               20031030
                                           US 2002-302932
                                                                  20021125
PRIORITY APPLN. INFO.:
                                           US 1998-79713P
                                                               P 19980326
                                           US 1998-80422P
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                                                                 19980402
                                           US 1998-81792P
                                                              Ρ
                                                                 19980415
                                           US 1998-82056P
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                                                                  19980416
                                           US 1998-89397P
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                                                                  19980615
                                                              P 19980616
                                           US 1998-89521P
                                           US 1998-98783P
                                                              P 19980901
                                           WO 1999-US6468
                                                              W 19990326
                                           US 1999-283657
                                                              A3 19990401
OTHER SOURCE(S):
                       MARPAT 131:257441
GI
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The invention relates to certain indolinone-based and pyrazolylamide-based compds., I and II, their method of synthesis, and combinatorial libraries consisting of the compds. [wherein AB = atoms to make up 1-2 fused and/or connected rings; R = aromatic or heteroarom. ring which may form an addnl. ring by cyclization to the methylene group; R1, R2 = H, alkyl, (hetero)aryl or -aliphatic ring, amino, NO2, halo, etc.; R3 = (un)substituted Ph; Z = (un) substituted (CH2)0-3; R4, R5 = H, alkyl, (hetero) aryl or -aliphatic, amine, ketone, etc.]. The invention also relates to methods of modulating the function of protein kinases using these compds., and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways. Data for prepns. and/or biol. activity are given, as well as the prepns. of various oxindole intermediates. For instance, the pyrazolecarboxamide derivative III gave up to 70% inhibition of growth of Calu-6 human lung carcinoma cells as a xenograft in mice. As another example, the indolinone derivative IV was prepared by condensation of 6-(4-methoxyphenyl)-2-oxindole with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde in the presence of piperidine. Extensive tests of a few selected compds. against a variety of protein kinases are described.

L62 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

1998:747592 CAPLUS

DOCUMENT NUMBER:

130:3771

TITLE:

Preparation of 3-(hetero)arylmethylidene-2-indolinone derivatives as modulators of protein kinase activity

for use in treating cancer.

INVENTOR(S):

Tang, Peng Cho; Sun, Li;

McMahon, Gerald; Shawver, Laura Kay;

Hirth, Klaus Peter

PATENT ASSIGNEE(S):

Sugen, Inc., USA

SOURCE:

PCT Int. Appl., 269 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.

KIND DATE

APPLICATION NO.

DATE

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WO 9850356
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             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
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                                  20040603
                                              US 2003-725267
                                                                       20031202
PRIORITY APPLN. INFO.:
                                              US 1997-45838P
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                                               US 1997-50977P
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                                                                    A3 19980507
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                                                                    A3 19980619
                                              US 1998-99721
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                                                                    A3 19980925
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                                                                    A3 20000112
                                               US 2000-516948
                                                                   B1 20000301
                                              US 2001-819698
                                                                   A3 20010329
OTHER SOURCE(S):
                         MARPAT 130:3771
GI
```

AB Title compds. [I; A1-A4 = C, N; when any of A1-A4 = N, then the corresponding R3-R6 = null; R1 = H, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, trihalomethylcarbonyl, OH, CO2H, trihalomethylsulfonyl, etc.; R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclyl, halo; R3-R6 = H, alkyl, trihalomethyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclyl, OH, SH, alkoxy, aryloxy, amino, phosphonyl, guanidinyl, NO2, halo, (iso)cyanato, etc.; R3R4 or R4R5 or R5R6 = cycloalkyl, aryl, heteroaryl, heteroalicyclyl, OCH2O, OCH2CH2O; Q = specified (substituted) (hetero)aryl; Z = O, S], were prepared Thus, 3-(4-imidazolylmethylidenyl)-4,6-dimethyl-2-indolinone inhibited CDK2 with IC50 = <0.78 μΜ.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L62 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:147306 CAPLUS

DOCUMENT NUMBER: 128:204803

TITLE: Indolinone combinatorial libraries and related

products and methods for the treatment of disease

INVENTOR(S): Tang, Peng Cho; Sun, Li;

McMahon, Gerald; Hirth, Klaus Peter;

Shawver, Laura Kay; et al.

PATENT ASSIGNEE(S): Sugen, Inc., USA; Tang, Peng Cho; Sun, Li; McMahon,

Gerald

SOURCE: PCT Int. Appl., 293 pp.

CODEN: PIXXD2

DOCUMENT TYPE: LANGUAGE: Patent English

FAMILY ACC. NUM. COUNT: 12

PATENT INFORMATION:

PA	rent :	NO.			KIND DATE					APPL	ICAT		DATE				
		- -				-	- -								-		
WO	9807	695			A1		1998	0226	,	WO 1	997-	US14	736		1:	9970	820
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					FI,												
		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,
					SD,										UA,	ŪĠ,	US,
					ZW,												
	RW:				MW,												
		GB,	GR,	ΙE,	IT,	LU,	MC,	ΝL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,
		GN,	ΜL,	MR,	NΕ,	SN,	TD,	TG									
CN	1155	838			Α		1997	0730	(CN 1:	996-:	1906	16		1	9960	505
CA	2264	220			AA		1998	0226	(CA 1:	997-		19970820				
	EP 929520																
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	MC,	PT,

GΙ

IE, FI					
JP 2001503736	T2	20010321	JP 1998-510973		19970820
EP 1247803	A2	20021009	EP 2002-77564		19970820
EP 1247803	A3	20021016			
R: AT, BE, CH,	DE, DK	(, ES, FR,	GB, GR, IT, LI, LU,	NL, SI	E, MC, PT,
IE, FI					
AU 9741556	A1	19980306	AU 1997-41556	•	19970821
PRIORITY APPLN. INFO.:			US 1996-702232	A	19960823
			US 1996-31585P	P	19961205
			US 1996-31586P	P	19961205
	•		US 1996-31588P	P	19961205
			US 1996-32546P	P	19961205
			US 1996-32547P	P	19961205
			US 1997-45565P	P	19970505
			US 1997-45566P	P	19970505
			US 1997-45714P	P	19970505
			US 1997-45715P	P	19970505
			US 1997-46843P	P	19970505
			EP 1997-939480	A3	19970820
			WO 1997-US14736	W	19970820
OTHER SOURCE(S):	MARPAT	128:20480	93		

The invention relates to indolinone derivs. capable of modulating, regulating, and/or inhibiting protein kinase signal transduction. compds. are useful for the treatment of diseases related to unregulated protein kinase signal transduction, including cell proliferative diseases such as cancer, atherosclerosis, arthritis, and restenosis, and metabolic diseases such as diabetes. Inhibitors specific to the FLK protein kinase can be obtained by adding chemical substituents to the 3-[(indole-3yl)methylene]-2-indolinone system, in particular at the 1' position of the indole ring. Indolinone compds. that specifically inhibit the FLK and platelet derived growth factor protein kinases can harbor a tetrahydroindole or cyclopentano[b]pyrrole moiety. Indolinone compds. that are modified with substituents, particularly at the 5 position of the oxindole ring, can effectively activate protein kinases. This invention also features novel hydrosol. indolinone compds. that are tyrosine kinase inhibitors, and related products and methods. Approx. 1200 title compds., such as I, were prepared by combinatorial condensation of certain (un) substituted indolinones with aldehydes at the 3-position. I gave complete inhibition of MET kinase at chimeric MET receptors in vitro. REFERENCE COUNT: THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS

Ι

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:10 ON 19 AUG
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L63
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L64
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              8 FILE CAPLUS
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L72
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L73 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:
                        2005:122809 CAPLUS
DOCUMENT NUMBER:
                         142:197875
TITLE:
                         Preparation of 3-(5-sulfonylated pyrrol-2-ylmethylene)-
                         2-indolinone derivatives as kinase inhibitors
INVENTOR(S):
                         Tang, Peng Cho; Wei, Chung Chen; Xia, Yi
                        Sugen, Inc., USA
PATENT ASSIGNEE(S):
SOURCE:
                        U.S. Pat. Appl. Publ., 67 pp.
                         CODEN: USXXCO
DOCUMENT TYPE:
                         Patent
LANGUAGE:
                        English
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
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                         _ _ _ _
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    US 2005032871
                         A1
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                                                                   20030903
                                            US 2002-407350P
PRIORITY APPLN. INFO.:
                                                              P 20020903
OTHER SOURCE(S):
                        MARPAT 142:197875
GT
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The title compds. (I) or prodrugs or pharmaceutically acceptable AB salts thereof [wherein R1, R2 = H, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, CO2R11, CONR11R12, C(:S)NR11R12, COR11, S(:O)2R11, SO2NR11R12, P(:0) (OR11) (OR12); R3, R4, R5, R6, R8, R9 = H, halogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicylic, OH, OR11, SH; SR11, NR11R12, -S(:0)2R11, SO2NR11R12, $(\texttt{CH2}) \, \texttt{nCO2R11}, \quad (\texttt{CH2}) \, \texttt{nCONR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \quad -\texttt{NHCO2R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R11}, \quad (\texttt{CH2}) \, \texttt{nCONR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \quad -\texttt{NHCO2R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R11}, \quad (\texttt{CH2}) \, \texttt{nCONR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \quad -\texttt{NHCO2R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R11}, \quad (\texttt{CH2}) \, \texttt{nCONR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \quad -\texttt{NHCO2R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R11}, \quad (\texttt{CH2}) \, \texttt{nCONR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \quad \texttt{COR11}, \quad \texttt{NR11COR12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11COR12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11R12}, \quad \texttt{C(:S)} \, \texttt{NR11R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11COR12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11COR12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \quad \texttt{NR11R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R12}, \\ \\ (\texttt{CH2}) \, \texttt{nCO2R1$ -OCO2R11, -OCONR11R12, cyano, NO2, wherein said aryl, heteroaryl and heteroalicyclic groups may be further substituted with alkyl or halogen; wherein n -3; R7 = H, alkyl, cycloalkyl, aryl, heteroaryl, OH, cyano, OR11, -CO2OR11, CONR11R12; R10 = alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, NR11R12, OR11, wherein said aryl group may be substituted with a substituent selected from the group consisting of -C(0)OR11, alkyl or halo; R11, R12 = H, alkyl, cycloalkyl, aryl, heteroaryl or heteroalicyclic, wherein said alkyl or aryl group may be substituted with one or more substituents selected from the group consisting of alkyl, aryl, hydroxy, amino, alkoxy, heteroalicyclic, carbonyl, carboxylic acid and carboxylic ester; alternatively, NR11R12 = (un) substituted 5-7 membered heteroalicyclic or 5-6 membered heteroaryl ring] are prepared These compds. modulate protein kinase activity and are useful in treating disorders related to abnormal kinase activity, in particular various cancers such as pancreatic cancer, breast cancer, lung cancer, laryngeal cancer, ovarian cancer, uterine cancer, skin cancer, prostate cancer, kidney cancer, colon cancer and testicular cancer. Pharmaceutical compns. comprising these compds., methods of treating diseases utilizing pharmaceutical compns. comprising these compds. and methods of preparing them are also disclosed. Thus, a mixture of oxindole, 3-[[4-[2-(dimethylcarbamoyl)ethyl]-5-formyl-2methyl-1H-pyrrol-3-yl]sulfonyl]benzoic acid (1 equiv) and piperidine (excess) in ethanol (0.2 M) was stirred at between room temperature to 100°. After completion, the mixture was concentrated and then triturated with dilute HCl solution to give 3-[[4-[2-(dimethylcarbamoyl)ethyl]-2-methyl-5-[((3Z)-2-oxo-1,2-dihydroindol-3-ylidene)methyl]-1H-pyrrol-3yl]sulfonyl]benzoic acid.

L73 ANSWER 2 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: DOCUMENT NUMBER:

2005:243075 BIOSIS PREV200510030554

Ι

TITLE:

Inhibition of platelet-derived growth factor signaling

AUTHOR (S):

attenuates pulmonary fibrosis.
Abdollahi, Amir; Li, Minglun; Ping, Gong; Plathow,

Christian; Domhan, Sophie; Kiessling, Fabian; Lee, Leslie

B.; McMahon, Gerald; Groene, Hermann-Josef;

Lipson, Kenneth E.; Huber, Peter E. [Reprint Author]

German Canc Res Ctr, Dept Radiat Oncol, D-69120 Heidelberg, CORPORATE SOURCE:

Germany

p.huber@dkfz.de

SOURCE: Journal of Experimental Medicine, (MAR 21 05) Vol. 201, No.

6, pp. 925-935.

CODEN: JEMEAV. ISSN: 0022-1007.

DOCUMENT TYPE:

Article English

LANGUAGE: ENTRY DATE:

Entered STN: 29 Jun 2005

Last Updated on STN: 29 Jun 2005

Pulmonary fibrosis is the consequence of a variety of diseases with no satisfying treatment option. Therapy-induced fibrosis also limits the efficacy of chemotherapy and radiotherapy in numerous cancers. Here, we studied the potential of platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitors (RTKIs) to attenuate radiation-induced pulmonary fibrosis. Thoraces of C57BL/6 mice were irradiated (20 Gy), and mice were treated with three distinct PDGF RTKIs (SU9518, SU11657, or Imatinib). Irradiation was found to induce severe lung fibrosis resulting in dramatically reduced mouse survival. Treatment with PDGF RTKIs markedly attenuated the development of pulmonary fibrosis in excellent correlation with clinical, histological, and computed tomography results. Importantly, RTKIs also prolonged the life span of irradiated mice. We found that radiation up-regulated expression of PDGF (A-D) isoforms leading to phosphorylation of PDGF receptor, which was strongly inhibited by RTKIs. Our findings suggest a pivotal role of PDGF signaling in the pathogenesis of pulmonary fibrosis and indicate that inhibition of fibrogenesis, rather than inflammation, is critical to antifibrotic treatment. This study points the way to a potential new approach for treating idiopathic or therapy-related forms of lung fibrosis.

L73 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:857170 CAPLUS

DOCUMENT NUMBER: 141:350032

TITLE:

Preparation of 5-sulfonamido-substituted indolinone

compounds as protein kinase inhibitors Tang, Peng Cho; Liang, Congxin; Miller,

Todd; Lipson, Kenneth E.

PATENT ASSIGNEE(S): Sugen Inc., USA

U.S. Pat. Appl. Publ., 58 pp. SOURCE:

CODEN: USXXCO Patent

DOCUMENT TYPE:

INVENTOR (S):

English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE _ _ _ _ -----US 2004204407 A1 20041014 US 2004-793952 20040308 PRIORITY APPLN. INFO.: US 2003-452552P P 20030307

OTHER SOURCE(S): MARPAT 141:350032

GI

$$\begin{array}{c|c} C1 & & & O \\ & & & Me \\ & & N \\ & N \\ & & N \\ & N$$

ΑB The title compds. [I; R1 and R2 combine to form (un) substituted optionally fused heterocyclic ring; R3-R5 = H, alkyl, hydroxyalkyl, etc.; or R3 and R4 may combine to form a cyclic 6-membered alicyclic ring which may be substituted with one or more lower alkyl] that modulate the activity of protein kinases ("PKs") and are therefore useful in treating disorders related to abnormal PK activity (no biol. data), were prepared General method of synthesis of the compds. I by condensation of oxindoles and aldehydes (preparation of intermediates is given) is described. Eighty-two compds. I (e.g., II) were prepared Pharmaceutical compns comprising the compds. I, methods of treating diseases utilizing pharmaceutical compns. comprising these compds. and methods of preparing them are also disclosed.

II

L73 ANSWER 4 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:379167 BIOSIS DOCUMENT NUMBER: PREV200300379167

TITLE: SU11248 maintenance therapy prevents tumor regrowth after

fractionated irradiation of murine tumor models.

Schueneman, Aaron J.; Himmelfarb, Eric; Geng, Ling; Tan, AUTHOR (S):

Jiahua; Donnelly, Edwin; Mendel, Dirk; McMahon, Gerald; Hallahan, Dennis E. [Reprint Author]

CORPORATE SOURCE: Department of Radiation Oncology, Vanderbilt University,

1301 22nd Avenue South, B-902 The Vanderbilt Clinic,

Nashville, TN, 37232-5671, USA

Dennis.Hallahan@mcmail.vanderbilt.edu

SOURCE: Cancer Research, (July 15 2003) Vol. 63, No. 14, pp.

4009-4016. print.

ISSN: 0008-5472 (ISSN print).

DOCUMENT TYPE: LANGUAGE:

Article English

ENTRY DATE:

Entered STN: 20 Aug 2003 Last Updated on STN: 20 Aug 2003

AB Receptor tyrosine kinase activation contributes to cell viability during cytotoxic therapy. The novel broad spectrum receptor tyrosine kinase inhibitor, SU11248, inhibits vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, c-kit, and fetal liver tyrosine kinase 3. In this study, we maintained SU11248 plasma levels beyond the completion of radiotherapy to determine whether tumor regrowth can be delayed. The antiangiogenic effects of SU11248 were demonstrated using human umbilical vein endothelial cells in vitro. Apoptosis increased and clonogenic survival decreased when SU11248 was used in combination with radiation from 0 to 6 Gy on endothelial cells. In vivo tumor growth delay was increased in C57B6J mice with Lewis lung carcinoma or glioblastoma multiform (GL261) hind limb tumors. Mice were treated with daily i.p. injections (40 mg/kg) of SU11248 during 7 days of radiation treatment (21 Gy). Combined treatment with SU11248 and radiation significantly reduced tumor volume as compared with either treatment alone. Concomitant reduction in vasculature was confirmed using the dorsal vascular window model. The vascular length established using images taken from a consistent quadrant in the window show the combination therapy was more effective in destroying tumor vasculature than either treatment alone. SU11248 maintenance administration beyond the completion of radiotherapy results in prolongation of tumor control. In summary, SU11248 enhances radiation-induced endothelial cytotoxicity, resulting in tumor vascular destruction and tumor control when combined with fractionated radiotherapy in murine tumor models. Moreover, inhibition of angiogenesis well beyond radiation therapy may be a promising treatment paradigm for refractory human neoplasms.

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L73 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:
                         2002:927188 CAPLUS
DOCUMENT NUMBER:
                         138:14005
TITLE:
                         Preparation of 5-aralkylsulfonyl-3-(pyrrol-2-
                         ylmethylidene)-2-indolinone derivatives as kinase
                         inhibitors
                         Cui, Jingrong; Ramphal, Yudhi; Liang, Congxin;
INVENTOR(S):
                         Sun, Li; Wei, Chung Chen; Tang, Peng
PATENT ASSIGNEE(S):
                         USA
SOURCE:
                         PCT Int. Appl., 479 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:
                         Patent
LANGUAGE:
                         English
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FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	TENT	NO.			KIN	D	DATE			APPL	ICAT	ION I	NO.		D	ATE				
WO	2002	0963	61		A2	_	2002	1205		WO 2	002-	US16	841		2	0020	530			
WO	2002	0963	61		A3	٠	2003	0313												
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							DK,													
							IN,													
	LS, LT, LU					MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	OM,	PH,			
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		UA,	UG,	US,	UΖ,	VN,	ΥU,	ZA,	ZM,	ZW,	AM,	ΑZ,	BY,	KG,	ΚZ,	MD,	RU,			
		ТJ,	TM																	
	RW:	GH,	GM,	KΕ,	LS,	MW,	ΜZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AT,	BE,	CH,			
	RW: GH, GM, KE CY, DE, DK					FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,			
	BF, BJ, CF					CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG			
US							A1 20030			US 2	002-	1570	07							
US	US 6599902						2003	0729												
PRIORIT	IORITY APPLN. INFO.:										US 2001-294544P						P 20010530			

US 2001-328408P P 20011010

OTHER SOURCE(S):

MARPAT 138:14005

$$\mathbb{R}^{3}$$
 \mathbb{R}^{4}
 \mathbb{R}^{5}
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 \mathbb{R}^{7}
 \mathbb{R}^{8}
 \mathbb{R}^{9}
 \mathbb{R}^{9}
 \mathbb{R}^{9}

AB The present invention relates to certain 5-aralkylsulfonyl-3-(pyrrol-2ylmethylidene)-2-indolinone derivs. (shown as I; see below for variable definitions; e.g. 2,4-dimethyl-5-(2-oxo-5-phenylmethanesulfonyl-1,2dihydroindol-(3Z)-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide) that inhibit kinases (no data), in particular met kinase. Pharmaceutical compns. comprising these compds., methods of treating diseases mediated by kinases using pharmaceutical compns. comprising these compds., and methods of preparing them are also disclosed. In I: n = 0-2; m = 1-3; R1 and R2 = H or alkyl; R3, R4, and R5 = H, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxy, cyano, carboxy, carboxyalkyl, nitro, aryl, aryloxy, heteroaryl, heteroaryloxy, -(alkylene)-CONR10R11, -CONR10R11, or - NR10R11 (R10 is H or alkyl, and R11 is aryl, heteroaryl, heterocycle, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, aralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy, or R10 and R11 together with the N atom to which they are attached combine to form saturated or unsatd. heterocycloamino). R6 is H, alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, heterocyclylalkyl, aryl, heteroaryl, carboxy, alkoxycarbonyl, heterocyclylcarbonyl, aminoalkylcarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, -CONR10R11 or -(alkylene)-CONR10R11. R7 and R8 = H, alkyl, cycloalkyl, heterocyclylalkyl, -COR12, -(alkylene)-COR12 (R12 = alkoxy, hydroxy, or heterocycle, alkylamino, dialkylamino), -SO2R14, -CONR13R14, or -(alkylene)-CONR13R14 (R13 is H or alkyl, and R14 is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, heteroaralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy group(s), or when R13 and R14 are attached to a N atom R13 and R14 together with the N atom to which they are attached form saturated or unsatd. heterocycloamino). R6 and R7 or R7 and R8 can combine to form a saturated or unsatd. 5 to 8 membered ring; and R9 is: H or alkyl; -PO(OR15)2 where each R15 = H or alkyl; -COR16 where R16 is H or alkyl; or -CHR17NR18R19 where R17 is H or alkyl, and R18 and R19 = H or alkyl or R18 and R19 together with the N atom to which they are attached form heterocycloamino. Although the methods of preparation are not claimed, 375 example prepns. of I

plus addnl. prepns. of intermediates are included.

L73 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2001:904107 CAPLUS

DOCUMENT NUMBER:

136:37505

TITLE:

Preparation of 3-(2-indolylmethylene)-2-indolinones as

protein kinase/phosphatase inhibitors for

treatment of proliferative diseases Tang, Peng Cho; Harris, G. Davis; Li,

INVENTOR(S): Xiaoyuan

PATENT ASSIGNEE(S):

Sugen, Inc., USA

SOURCE:

PCT Int. Appl., 199 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA'	TENT I	. 00			KIND DATE					APPL	ICAT	ION I	NO.	DATE					
					A2 20011213 A3 20020808					WO 2	001-	JS17	961		2	0010	604		
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											EE,								
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,		
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,		
		RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,		
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CA	2410	509			AA		2001	1213	(CA 2	001-2	2410		2	0010	504			
US	20020	0523	59		A1		2002	0502	1	US 2	001-	3717	20010604						
US	6706	709			B2		2004	0316											
EP	1294																		
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		ΙE,	SI,	LT,	LV,	FI,	RO,	MK,	CY,	ΑL,	TR								
JP	JP 2003535847						2003	1202		JP 2	002-	5018	62		2	00106	504		
US	US 2004147586						2004	0729	1	US 2	003-	7252	77		2	00312	202		
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									1	US 2	001-8	3717	00	7	A3 2	0010	504		
										WO 2001-US17961						W 20010604			
OTHER S	OURCE	(S):			MARPAT 136:37505				5										

GI

AΒ Title compds. I [wherein R4-R6 and R8-R10 = H; R1, R2, and R3 = independently H, halo, carboxylic acid, trihalomethyl, or (un) substituted ester, amide, alkyl, alkoxy, or (hetero)aryl; R7 = (un)substituted alkyl or alkoxy; or pharmaceutically acceptable salt thereof] were prepared as modulators of the activity of protein kinases (PKs) and phosphatases. For example, 5-bromo-2-oxindole was coupled with 5-(3-diethylaminopropyl)-1H-indole-2-carbaldehyde (preparation given) in the presence of piperidine in EtOH to afford II, which inhibited GST-FLK-1, EGF receptor kinase, and PDGF with IC50 values of 0.03 $\mu M,~2.87~\mu M,$ and 0.38 μM , resp. I are useful in treating disorders related to abnormal PK activity, such as blood vessel proliferative disorders, mesangial cell proliferative disorders, fibrotic disorders, cancer, diabetes, autoimmune disorders, hyperproliferation disorders, restenosis, fibrosis, psoriasis, von Heppel-Lindau disease, osteoarthritis, rheumatoid arthritis, angiogenesis, inflammatory disorders, immunol. disorders, and cardiovascular disorders (no data). Combinatorial libraries comprising at least five indolinone compds., formed by reacting oxindoles with aldehydes, are also claimed.

II

Ι

L73 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2001:868415 CAPLUS

DOCUMENT NUMBER:

136:697

TITLE:

Mannich base prodrugs of 3-(pyrrol-2-ylmethylidene)-2-

indolinone derivatives

INVENTOR (S):

Moon, Malcolm Wilson; Morozowich, Walter; Gao, Ping;

Tang, Peng Cho

PATENT ASSIGNEE(S):

Sugen, Inc., USA; Pharmacia & Upjohn Company

SOURCE: PCT Int. Appl., 96 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO. APPLICATION NO. KIND DATE DATE

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WO 2001090068
                           A2
                                 20011129
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                                                                     20010524
     WO 2001090068
                           A3
                                 20020606
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
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                          A1
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                                                                     20010524
     US 6482848
                          B2
                                 20021119
     EP 1301507
                          A2
                                 20030416
                                             EP 2001-939357
                                                                     20010524
             AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
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                                 20031118
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     US 2003083363
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                                 20030501
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PRIORITY APPLN. INFO.:
                                             US 2000-207000P
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                                             US 2000-225045P
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                                             US 2001-863819
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                                             WO 2001-US16757
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                                             US 2002-243663
                                                                  A1 20020916
                                             US 2002-243942
OTHER SOURCE(S):
                         MARPAT 136:697
     The present invention is directed to Mannich base prodrugs of certain
     3-(pyrrol-2-ylmethylidene)-2-indolinone derivs. that modulate the activity
     of protein kinases ("PKs"). Pharmaceutical compns.
     comprising these compds., methods of treating diseases
     related to abnormal PK activity utilizing pharmaceutical
     compns. comprising these compds. and methods of preparing them are
     also disclosed.
L73 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:
                         2001:617993 CAPLUS
DOCUMENT NUMBER:
                         135:195497
TITLE:
                         Preparation of pyrrole substituted 2-indolinone
                         protein kinase inhibitors for treatment of cancer
INVENTOR(S):
                         Tang, Peng Cho; Miller, Todd; Li, Xiaoyuan;
                         Sun, Li; Wei, Chung Chen; Shirazian, Shahrzad;
                         Liang, Congxin; Vojkovsky, Tomas; Nematalla, Asaad S. Sugen, Inc., USA
PATENT ASSIGNEE(S):
                         PCT Int. Appl., 225 pp.
SOURCE:
                         CODEN: PIXXD2
DOCUMENT TYPE:
                         Patent
LANGUAGE:
                         English
FAMILY ACC. NUM. COUNT:
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Page 24
PATENT INFORMATION:

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	20010									BR	2001	-8394			2	0010	215
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BG :					A							-1070				0020	
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	20051				A1		2005	0811		US	2005	-2847	7		2	0050	104
PRIORITY	APPI	LN.								US	2000	-1827	10P		P 2	0000	215
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						•				US	2000	-2435	32P		P 2	0001	027
										US	2001	-7832	64		A3 2	0010	215
												-AU48					
										WO	2001	-US48	13		W 2	0010	215
										US	2003	-4126	90		A1 2	0030	414
OTHER SOU	URCE	(S) :			MARI	PAT	135:	19549	7								

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 R^6
 R^7
 R^6
 R^7
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 R^7
 R^6

ΑB The title compds. (I) [wherein R1 = H, halo, (cyclo)alkyl, (hetero)aryl, heteroalicyclic, OH, alkoxy, acyl, (un) substituted amino or carbamoyl, etc.; R2 = H, halo, alkyl, trihalomethyl, OH, alkoxy, CN, (hetero)aryl, (un) substituted amino, acyl (amino), or sulfamoyl, etc.; R3 = H, halo, alkyl, trihalomethyl, OH, alkoxy, (hetero)aryl, (un)substituted acyl, (acyl)amino, sulfamoyl, or alkylsulfonyl, etc.; R4 = H, halo, alkyl, OH, alkoxy, or (un)substituted amino; R5 and R6 = independently H, alkyl, or acyl; R7 = H, alkyl, (hetero)aryl, or acyl; and their pharmaceutically acceptable salts] were prepared as protein kinase modulators for the treatment of cellular disorders such as cancer. For example, 5-fluoro-1,3-dihydroindol-2-one was condensed with 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2diethylaminoethyl)amide to give II (55%). II exhibited comparable activity against Flk-1 and PDGFRB and inhibited PDGF-dependent receptor phosphorylation in cells with an IC50 value of approx. 0.03 μΜ. In efficacy expts. against various cancers in mice, II was well tolerated at 80 mg/kg/day, even when dosed continuously for more than 100

II

Ι

L73 ANSWER 9 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN ACCESSION NUMBER: 2002:143055 BIOSIS

ACCESSION NUMBER: DOCUMENT NUMBER:

PREV200200143055

TITLE:

TSU-68 (SU6668), an anti-angiogenic agent, shows stronger anti-tumor effects against higher VEGF productive and more hypervascular tumors, which are poor prognostic factors in

breast cancers.

AUTHOR(S):

Chikahisa, L. [Reprint author]; Yonekura, K.; Basaki, Y.; Fujita, H.; Hashimoto, A.; Cherrington, J.; Shawver,

L. K.; Yamada, Y.; Kitazato, K.

CORPORATE SOURCE:

Cancer Research Laboratory, Taiho Pharmaceutical Co., Ltd.,

Hanno, Saitama, Japan

SOURCE:

Breast Cancer Research and Treatment, (October, 2001) Vol.

69, No. 3, pp. 283. print.

Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.

CODEN: BCTRD6. ISSN: 0167-6806.

DOCUMENT TYPE:

Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

Conference; (Meeting Poster)

LANGUAGE:

English

ENTRY DATE:

Entered STN: 14 Feb 2002

Last Updated on STN: 26 Feb 2002

L73 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2002:628660 CAPLUS

DOCUMENT NUMBER:

137:346843

TITLE:

Effects of vascular endothelial and platelet-derived

growth factor receptor inhibitors on long-term

cultures from normal human bone marrow

AUTHOR (S):

Duhrsen, Ulrich; Martinez, Tanja; Vohwinkel, Gabi;

Ergun, Suleyman; Sun, Li; McMahon,

Gerald; Durig, Jan; Hossfeld, Dieter Kurt;

Fiedler, Walter

CORPORATE SOURCE:

Zentrum fur Innere Medizin, Abteilung fur Hamatologie,

Universitatsklinikum Essen, Germany Growth Factors (2001), 19(1), 1-17

SOURCE:

CODEN: GRFAEC; ISSN: 0897-7194

PUBLISHER:
DOCUMENT TYPE:

Taylor & Francis Ltd.
Journal

DOCUMENT TYPE LANGUAGE:

English

AB Endothelial cells and fibroblasts are important constituents of the hemopoietic microenvironment. Growth and function of these cells are controlled by a variety of cytokines, including VEGF and PDGF. The authors analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compds. SU5614 and SU5768) on the performance of long-term cultures from normal human bone marrow. In developing cultures, the inhibitors induced a dose-dependent reduction in stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell production and an increase in fat cells. For SU5614, the concentration

inhibiting stroma formation by 50% (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the resp. values were 871 nM and 331 nM. Changes in stroma composition and inhibition of hemopoietic cell production were also demonstrable after delayed addition of the inhibitors to established cultures. By contrast, hemopoietic colony formation in clonogenic agar cultures was unimpaired (IC50 not reached at 100 µM). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was associated with decreased levels in conditioned media of granulocyte-macrophage colony-stimulating factor, interleukin-6 and leptin. VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have therapeutic potential in stroma diseases such as myelofibrosis. Since they weaken the stimulatory signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases. REFERENCE COUNT: THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 11 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

ACCESSION NUMBER: 2001:301449 BIOSIS DOCUMENT NUMBER: PREV200100301449

TITLE: Effects of vascular endothelial and platelet-derived growth

factor receptor inhibitors on long-term cultures from

normal human bone marrow.

Duehrsen, U. [Reprint author]; Sun, Li; AUTHOR (S):

McMahon, G.; Duerig, J. [Reprint author]; Fiedler,

CORPORATE SOURCE:

University Hospital, Essen, Germany Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. SOURCE:

308a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December

01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 27 Jun 2001

Last Updated on STN: 19 Feb 2002

Bone marrow endothelial cells and fibroblasts are critically involved in the regulation of blood cell production. Growth and function of endothelial cells and fibroblasts are controlled by a variety of cytokines, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). We analyzed the effects of novel tyrosine kinase inhibitors targeting the VEGF and PDGF receptors (compounds SU5614 and SU5768) on the performance of human long-term marrow cultures. In developing cultures, the inhibitors induced a dose-dependent reduction in the numbers of stromal fibroblasts, macrophages and endothelial cells with a concomitant decrease in blood cell production and an increase in fat cells. For SU5614, the concentration inhibiting stroma formation by 50 % (IC50) was 123 nM, and the IC50 for hemopoietic colony forming cell output was 186 nM. For SU5768, the respective values were 871 nM and 331 nM. Changes in stroma composition and inhibition of hemopoietic cell production were also demonstrable after delayed addition of the inhibitors to established cultures. By contrast, hemopoietic colony formation in agar cultures was unimpaired (IC50 not reached at 100 muM). Immunofluorescence studies and time course analyses suggested that the primary effect of the inhibitors was interference with the proliferation and function of fibroblasts and endothelial cells which in turn resulted in decreased hemopoiesis and increased adipogenesis. This was associated with decreased levels in conditioned media of various hemopoiesis-stimulating cytokines. Thus, VEGF and PDGF may play a hitherto underestimated role in the control of blood cell formation. VEGF/PDGF receptor inhibitors may have therapeutic potential in stroma diseases such as myelofibrosis. Since the inhibitors weaken the hemopoiesis-stimulating signals provided by the microenvironment, they may also be of value in the treatment of leukemia and other neoplastic bone marrow diseases.

L73 ANSWER 12 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:21857 BIOSIS DOCUMENT NUMBER: PREV200000021857

TITLE: First preclinical and clinical results with the

antiangiogenetic substance SU 5416 in malignancies.

AUTHOR (S): Scigalla, Paul [Reprint author]; Hannah, Alison [Reprint

author]; Langecker, Peter [Reprint author]; Shawver, Laura [Reprint author]; McMahon, Jeromy [Reprint

author]; Hirth, Peter [Reprint author]

CORPORATE SOURCE: SUGEN Inc., San Francisco, CA, USA

SOURCE:

European Journal of Cancer, (Oct., 1999) Vol. 35, No.

SUPPL. 5, pp. S62. print.

Meeting Info.: 5th International Symposium on the Biological Therapy of Cancer: From Basic Research to Clinical Applications. Munich, Germany. October 27-30, 1999. Biological Therapeutics Development Group of the European Organisation for Research and Treatment of Cancer.

CODEN: EJCAEL. ISSN: 0959-8049.

DOCUMENT TYPE:

Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE:

English

ENTRY DATE:

Entered STN: 29 Dec 1999

Last Updated on STN: 31 Dec 2001

L73 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN

1997:640690 CAPLUS

ACCESSION NUMBER: DOCUMENT NUMBER:

127:314804

TITLE:

Assays for KDR/FLK-1 receptor tyrosine kinase

inhibitors, and use of the inhibitors for

treatment of vasculogenesis- and angiogenesis-related diseases

INVENTOR(S):

Hirth, Klaus P.; McMahon, Gerald; Shawver, Laura K.

PATENT ASSIGNEE(S):

Sugen, Inc., USA

SOURCE:

PCT Int. Appl., 65 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA'	rent :	NO.			KIND DATE					APPL	ICAT	NO.	DATE				
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WO	9734	920			A1		1997	0925	1	WO 1	997-1	US33'	78		1:	9970:	304
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	MN, MX, NO				ΝZ,	ΡL,	RO,	RU,	SG,	SI,	SK,	TJ,	TM,	TR,	TT,	UA,	UΖ,
	VN, YU, AM			AM,	ΑZ,	ΒY,	KG,	KΖ,	MD,	RU,	TJ,	TM					
	RW:	GH,	KΕ,	LS,	MW,	SD,	SZ,	UG,	ΑT,	BE,	CH,	DE,	DK,	ES,	FI,	FR,	GB,
		GR,	ΙE,	ΙT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,
	ML, MR, NE, S					TD,	TG										
AU		A1		1997	1010	AU 1997-20667						19970304					
PRIORITY APPLN. INFO.:									1	US 1:	996-	6217	34	7	A 1:	9960	321
						1	WO 1	997-1	1533	78	Ţ	ω 1 ·	9970	304			

AB Processes are disclosed for the identification of compds. and pharmaceutical compns. capable of selectively and potently inhibiting KDR/FLK-1 tyrosine kinase signal transduction in order to inhibit vasculogenesis and/or angiogenesis. The invention also relates to compds. and compns. identified using the methods of the invention and the use thereof for the treatment of disease relating to inappropriate vasculogenesis and/or angiogenesis. The invention provides an assay cascade comprised of several "filter steps" of increasing selectivity which identify a limited subset of candidate compds. affecting the VEGF receptor on the mol. level.

=> dis his

(FILE 'HOME' ENTERED AT 14:56:18 ON 19 AUG 2005)

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Page 29
     FILE 'REGISTRY' ENTERED AT 14:58:18 ON 19 AUG 2005
L1
                STR
L2
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              1 S L1 FUL
L3
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L4
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L5
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              0 FILE EMBASE
L6
L7
              1 FILE CAPLUS
     TOTAL FOR ALL FILES
L8
              1 S L3
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L9
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L10
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L11
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L13
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L14
            964 FILE EMBASE
L15
            522 FILE CAPLUS
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           1859 S L11
L16
        2428283 FILE MEDLINE
L17
L18
        3250801 FILE BIOSIS
L19
        1419137 FILE EMBASE
L20
        3099346 FILE CAPLUS
     TOTAL FOR ALL FILES
L21
       10197567 S (PHARMAC? OR COMBINATOR? LIBRAR? OR COMPOS?)
L22
             28 FILE MEDLINE
L23
            236 FILE BIOSIS
L24
            804 FILE EMBASE
            157 FILE CAPLUS
L25
     TOTAL FOR ALL FILES
L26
           1225 S L16 AND L21
L27
         186701 FILE MEDLINE
         365178 FILE BIOSIS
L28
L29
         145295 FILE EMBASE
         147528 FILE CAPLUS
L30
     TOTAL FOR ALL FILES
L31
         844702 S (TREAT? OR PREVENT? OR THERAP?) (5A) DISEASE?
L32
              1 FILE MEDLINE
L33
             81 FILE BIOSIS
             85 FILE EMBASE
L34
L35
             43 FILE CAPLUS
     TOTAL FOR ALL FILES
L36
            210 S L26 AND L31
L37
            447 FILE MEDLINE
L38
            676 FILE BIOSIS
L39
            302 FILE EMBASE
            943 FILE CAPLUS
L40
     TOTAL FOR ALL FILES
L41
           2368 S TANG P?/AU
           1354 FILE MEDLINE
L42
           1773 FILE BIOSIS
L43
L44
           1108 FILE EMBASE
           4875 FILE CAPLUS
L45
     TOTAL FOR ALL FILES
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p) 5

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Page 30
           9110 S SUN L?/AU
L46
L47
            122 FILE MEDLINE
L48
            223 FILE BIOSIS
L49
            106 FILE EMBASE
L50
            220 FILE CAPLUS
     TOTAL FOR ALL FILES
            671 S MCMAHON G?/AU
L51
L52
             53 FILE MEDLINE
L53
             99 FILE BIOSIS
             54 FILE EMBASE
L54
             65 FILE CAPLUS
L55
     TOTAL FOR ALL FILES
L56
            271 S SHAWVER L?/AU
L57
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L58
              2 FILE BIOSIS
L59
              O FILE EMBASE
L60
              3 FILE CAPLUS
     TOTAL FOR ALL FILES
L61
              5 S L41 AND L46 AND L51 AND L56
L62
              5 DUP REM L61 (0 DUPLICATES REMOVED)
L63
              O FILE MEDLINE
L64
              5 FILE BIOSIS
L65
              O FILE EMBASE
L66
             10 FILE CAPLUS
     TOTAL FOR ALL FILES
             15 S L36 AND (L41 OR L46 OR L51 OR L56)
L67
L68
              O FILE MEDLINE
L69
              5 FILE BIOSIS
L70
              O FILE EMBASE
L71
              8 FILE CAPLUS
     TOTAL FOR ALL FILES
L72
             13 S L67 NOT L61
L73
             13 DUP REM L72 (0 DUPLICATES REMOVED)
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     FILE 'REGISTRY' ENTERED AT 15:11:00 ON 19 AUG 2005
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=> log y
COST IN U.S. DOLLARS
                                                  SINCE FILE
                                                                  TOTAL
                                                       ENTRY
                                                                 SESSION
FULL ESTIMATED COST
                                                       46.05
                                                                 801.13
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)
                                                  SINCE FILE
                                                                  TOTAL
                                                       ENTRY
                                                                 SESSION
CA SUBSCRIBER PRICE
                                                                 -13.87
                                                       -8.03
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STN INTERNATIONAL LOGOFF AT 15:13:25 ON 19 AUG 2005